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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/397,550 | 09/16/1999 | JASON PETER BROWN | A0000180-66- | 8892 |

7590 05/01/2002
WARNER-LAMBERT COMPANY
2800 PLYMOUTH ROAD
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EXAMINER

MURPHY, JOSEPH F

| ART UNIT | PAPER NUMBER |
|----------|--------------|
|----------|--------------|

1646

DATE MAILED: 05/01/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application N . | Applicant(s) | |
| | 09/397,550 | BROWN ET AL. | |
| | Examiner | Art Unit | |
| | Joseph F Murphy | 1646 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 March 2001.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 8 and 10-23 is/are pending in the application.
- 4a) Of the above claim(s) 8 and 13-22 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 10-12 and 23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>11</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Formal Matters

Claims 5, 6, 7, 9 were cancelled, and claims 2, 3, 4 were amended, and new claim 23 was added in Paper No. 12, 2/25/2002. Claims 8, 13-22 stand withdrawn from consideration pursuant to 37 CFR 1.142(b). Claims 1-4, 10-12 and 23 are under consideration.

Specification

The disclosure is objected to because of the following informalities: According to 37 CFR 1.821(d) (MPEP § 2422), where the description or claims of a patent application discuss a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application. Sequences appear, *inter alia*, on page 9, lines 35-38, of the specification but are not identified by "SEQ ID NO" as required. The use of "SEQ ID N°" is not in compliance with the requirements of 37 CFR 1.821(d).

Appropriate correction is required.

Response to Amendment

Applicant's arguments and amendments of Paper No. 12, 2/25/2002 have been fully considered, but are not persuasive, for the reasons et forth below.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 12 stand rejected under 35 U.S.C 112, first paragraph, because the specification, while being enabling for nucleotides encoding SEQ ID NO: 20 and 22, does not reasonably provide enablement for a nucleic acid encoding any other polypeptide, for reasons of record set forth in Paper No. 8, 3/7/2001. There is not adequate guidance as to the nature of the polypeptide which Applicants claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with this claim.

The rejection of record set forth that Claims 1 and 12 are overly broad in the recitation of "alpha2delta-2" etc., since no guidance as to what constitutes " alpha2delta-2" etc. polypeptide is provided within the claims. The broad scope of claims 1 and 12 can be read to encompass a polynucleotide encoding any isolated polypeptide. There is no guidance provided in the specification as to how one of ordinary skill in the art would generate a nucleic acid encoding a polypeptide other than those exemplified in the specification.

Applicant argues that truncated alpha2delta-2 etc. subunits have been illustrated by three sequences and that the skilled artisan has enough guidance to create other deletion mutants which are secreted. However, as set forth in Paper No. 8, 3/7/2001, the court in In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 set forth that the test of enablement is not whether any experimentation

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is necessary, but whether, if experimentation is necessary, it is undue. The factors considered to be relevant in the instant case are discussed below:

- (1) the breadth of the claims - The instant claims are drawn to nucleic acids encoding voltage dependent calcium channel polypeptides.
- (2) the nature of the invention - The instant invention is a nucleic acid.
- (3) the state of the prior art - It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on an encoded protein's function.
- (5) the level of predictability in the art - Since the effect of a change of even a single amino acid can have dramatic effects on protein function, the art is unpredictable.
- (6) the amount of direction provided by the inventor - Applicant has only taught three nucleic acids encoding polypeptides which bind gabapentin.
- (7) the existence of working examples - Working examples are provided only for three nucleic acids encoding polypeptides which bind gabapentin.
- (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure - Based on the content of the disclosure and the breadth of claims 1 and 12 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use nucleic acids encoding voltage dependent calcium channel polypeptides.

Claims 2-3 stand rejected, and new claim 23 is rejected, under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide encoding a substantially purified polypeptide comprising an amino acid sequence set forth in SEQ ID NO: 20 and 22, does not reasonably provide enablement for a polynucleotide encoding a substantially purified variant having at least 90% amino acid sequence identity to SEQ ID NO: 20 and 22, for reasons of record set forth in Paper No. 8, 3/7/2001. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection of record set forth that claims 2-3, and 23 are overly broad in the recitation of "at least 90% identical" since no guidance is provided as to which of the myriad of polynucleotide species encoding polypeptide species encompassed by the claim will retain the characteristics of a voltage-dependent calcium channel. The specification provides insufficient guidance how to generate voltage-dependent calcium channels, and does not disclosing any actual or prophetic examples on expected performance parameters of any of the possible muteins of voltage-dependent calcium channels. However, it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Mikayama et al. (1993) teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically

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affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

There is insufficient guidance provided in the specification as to how one of ordinary skill in the art would generate a nucleic acid sequence encoding a voltage-dependent calcium channel other than those exemplified in the specification.

Applicant argues that the claims have been amended to clarify the types of substitutions which may be contemplated by the skilled person. However, the limitations added do not limit the "contemplated" substitutions, because the nucleic acid may encode "equivalent" amino acids. This term is indefinite (*infra*), and does not impose as limitation on the types or number of substitutions. The Wands factors considered to be relevant in the instant case are set forth below:

(1) the breadth of the claims - The instant claims are drawn to nucleic acids encoding voltage dependent calcium channel polypeptides.

(2) the nature of the invention - The instant invention is a nucleic acid.

(3) the state of the prior art - The Mikayama and Voet references demonstrate that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function.

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(5) the level of predictability in the art - The Mikayama and Voet references demonstrate the unpredictability of the protein art.

(6) the amount of direction provided by the inventor - Applicant has only taught three nucleic acids encoding polypeptides which bind gabapentin.

(7) the existence of working examples - Working examples are provided only for three nucleic acids encoding polypeptides which bind gabapentin.

(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure - Based on the content of the disclosure and the breadth of claims 2-3 and 23 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use a nucleic acid encoding a substantially purified variant having at least 90% amino acid sequence identity to SEQ ID NO: 20 and 22.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 1-4, 10-12 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 12 are indefinite in that they only describe the peptide of interest by an arbitrary protein name, i.e. "alpha2delta" etc, for reasons of record set forth in Paper No. 8, 3/7/2001. Applicant argues that the term "alpha2delta" etc. are known in the art, however, as set forth in the rejection of record, Applicant should particularly point out and distinctly identify the polypeptide by claiming structural characteristics associated with the protein (e.g. amino acid sequence, molecular weight, etc.). Identification of biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly designate what that protein is. No structural limitations are provided for the terms indicated, thus the metes and bounds of the claims cannot be determined.

The term "equivalent" in claims 2-3 is a relative term which renders the claim indefinite. The term "equivalent" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

The term "specificity" in claims 2-3 is a relative term which renders the claim indefinite. The term "specificity" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

The term "affinity" in claims 2-3 is a relative term which renders the claim indefinite. The term "affinity" is not defined by the claim, the specification does not provide a standard for

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ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4 and 10-12 stand rejected, and new claim 23 is rejected, under 35

U.S.C. 102(b) as being anticipated by Wei et al. (1998).

Wei et al. discloses a human alpha 2 calcium channel which is 100% identical to SEQ ID NO: 1 (See Sequence Comparison A, attached). This mRNA was cloned into a vector and expressed in host cells, thus anticipating claims 1, 4, and 10-12.

Applicant argues that Wei et al. teaches the full length calcium channel. However, the nucleic acid disclosed by Wei et al. still meets the limitations of the claims, since claims 4 and 23 use open language to describe the nucleic acid sequence, and claim 1 is indefinite in the description of the nucleic acid sequence.

Claims 1, 10-12 stand rejected, and new claim 23 is rejected, under 35 U.S.C. 102(b) as being anticipated by WO 9504822 (Harpold et al.).

Harpold et al. discloses the cloning and expression of human voltage gated calcium channel subunits, thus anticipating claim 1. The polynucleotide encoding neuronal alpha 2

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polypeptide was cloned into an expression vector and transfected into host cells, and the expressed protein was isolated (page 86-88), thus anticipating claims 10-12.

Applicant argues that Harpold et al does not teach a nucleic acid encoding a soluble calcium channel. However, the nucleic acid taught by Harpold still meets the limitations of the claims because claim 23 uses open language to describe the nucleic acid sequence, and claim 1 is indefinite in the description of the nucleic acid sequence.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245.

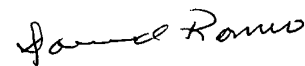
The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
April 29, 2002


DAVID S. ROMEO
PRIMARY EXAMINER